Using human genetic evidence to identify and develop medicines that make a difference in people's lives

March 22, 2016

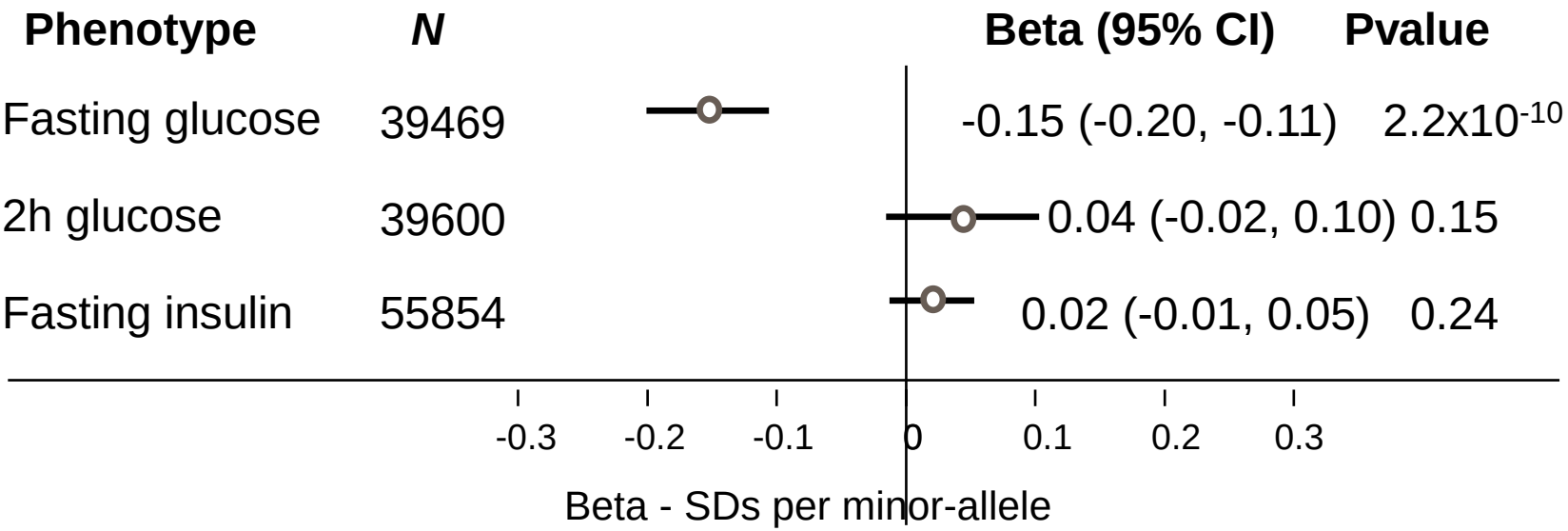
Meg Ehm on behalf of Genomic Resources for Drug Discovery Consortium

Background

- Using human genetic evidence to identify and develop medicines.
- Work is built on technology advances, understanding of biological pathways, genomics/genetics, progress in gene editing, informatics and emergence of large scale human health databases.
- Previous efforts assess the impact of genetic variation on clinical phenotypes have used population studies & genetic analysis consortiums
  - Phenotypes are reduced to a “common denominator” and rarely have longitudinal information.
  - Very few collections have drug usage and/or drug response information.
  - Research is slow
  - Many conditions haven’t been studied

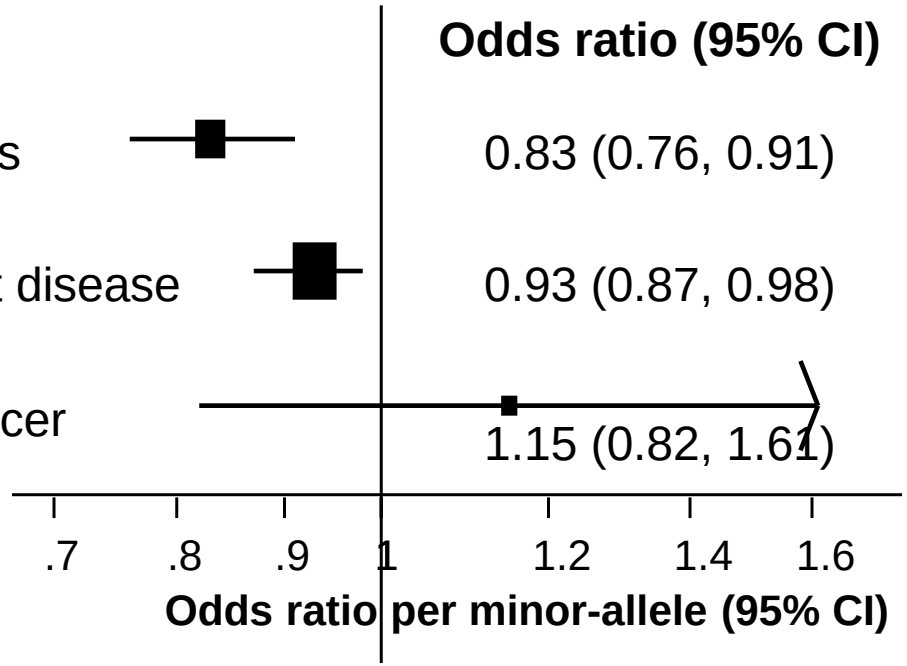
Example –Predicting Clinical Response

- Identified low-frequency missense variant (Ala316Thr) in *GLP1R* gene, the target of *GLP1R* agonists:



Association with clinical endpoints

- We investigated the association of the variant with other disease outcomes:



Outcome	Odds ratio (95% CI)	N_{cases}	$N_{controls}$	Pvalue
Type 2 diabetes	0.83 (0.76, 0.91)	25868	122393	$9.4x10^{-5}$
Coronary heart disease	0.93 (0.87, 0.98)	61846	163728	$9.2x10^{-3}$
Pancreatic cancer	1.15 (0.82, 1.61)	4987	8627	0.43

March 4, 2016 press release

Victoza® significantly reduces the risk of major adverse cardiovascular events in the LEADER trial

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Wish to study genetic influence of potential drug target genes on medically relevant traits

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 67, NO. 2, 2016

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Letters

Lipoprotein-Associated Phospholipase A_2 Loss-of-Function Variant and Risk of Vascular Diseases in 90,000 Chinese Adults

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 DECEMBER 5, 2013 VOL. 369 NO. 23

APOL1 Risk Variants, Race, and Progression of Chronic Kidney Disease

Personalized Medicine and Imaging
Clinical Cancer Research

Identification of a Variant in *KDR* Associated with Serum VEGFR2 and Pharmacodynamics of Pazopanib

Michael L. Maitland[1,2,3], Chun-Fang Xu[4], Yu-Ching Cheng[5], Emily Kistner-Griffi
Kathleen A. Ryan[5], Theodore G. Karrison[3,6], Soma Das[3,7], Dara Torgerson[7],
Eric R. Gamazon[8], Vasiliki Thomeas[1], Matthew R. Levine[1], Paul A. Wilson[9], Nan
Yuan Liu[11], Lon R. Cardon[12], Lini N. Pandite[13], Jeffrey R. O'Connell[5], Nancy J. C
Braxton D. Mitchell[5], Mark J. Ratain[1,2,3], and Alan R. Shuldiner[5,14]

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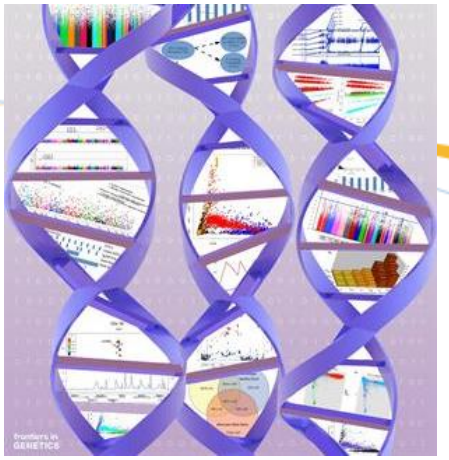
Cardiometabolic Risk

Genetic Inhibition of *CETP*, Ischemic Vascular Disease and Mortality, and Possible Adverse Effects

Trine Holm Johannsen, MD, PHD,*† Ruth Frikke-Schmidt, MD, DMSC,*† Jesper Schou, MSC,*†
Børge G. Nordestgaard, MD, DMSC,†‡§ Anne Tybjærg-Hansen, MD, DMSC*†§
Copenhagen, Denmark

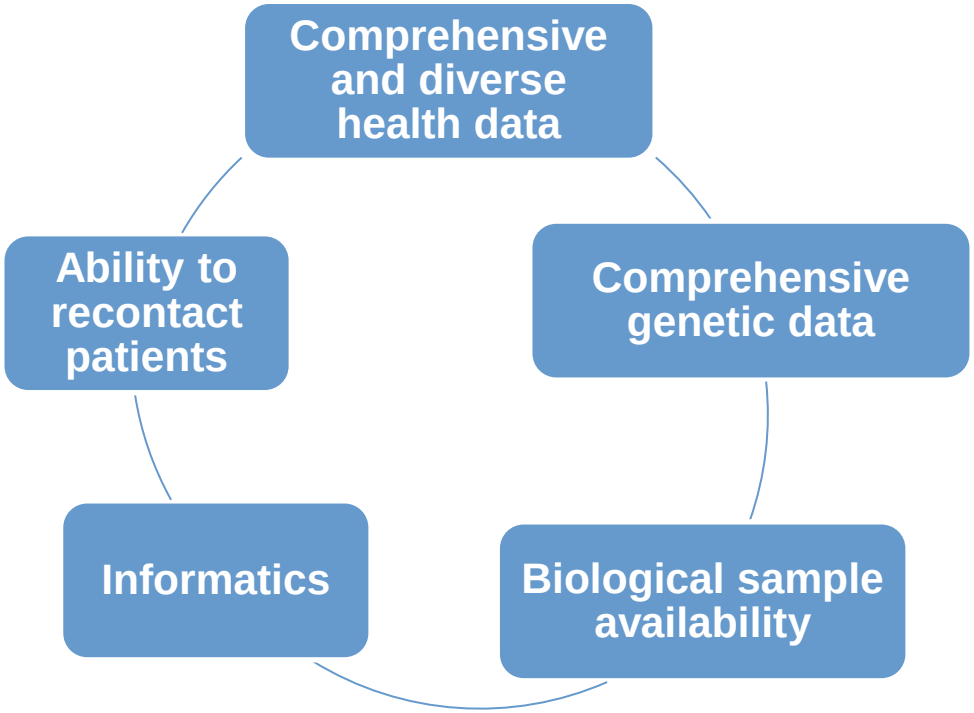
Potential of EMR-linked Biobanks to Influence Drug Discovery & Development



- EMR-linked biobanks enable study of clinical characteristics and healthcare utilization:
  - conditions not studied – RSV hospitalization
  - disease trajectories – heart failure->pulmonary edema->renal conditions
- Pharma companies envision using EMR-linked biobanks to:
  - Recruit patients for further study by phenotype or genotype.
  - Study of the effects of gene variants on clinical phenotypes which can anticipate effects of drug treatment.
  - Study the effect of gene variants on the trajectory of disease and use of the health care system supporting indication optimization.

Genomic Resources for Drug Discovery Consortium

- We see value in integrated medical and genomic resources to identify/prioritize targets and understand drug response:



Genomic Resources for Drug Discovery Consortium

- View developing a research enabled environment to facilitate work is a pre-competitive activity and will require more resources than any one company can provide.

- Agree it is critical to engage early in the design and development of genomic/EMR resources to leverage unique insight into use of resources for drug discovery and development questions.

- Agree that harmonization of multiple resources (ethnicities, health settings,…) will be needed to fully realize value – no one resource will be enough.

EMR-Linked Biobanks for Drug Discovery

Basic Research and Pre-Clinical Studies

Evidence that target is associated with outcomes

Minimal

Evidence that target contributes to disease progression.

Differentiating

Evidence that modulating target impacts disease & progression.

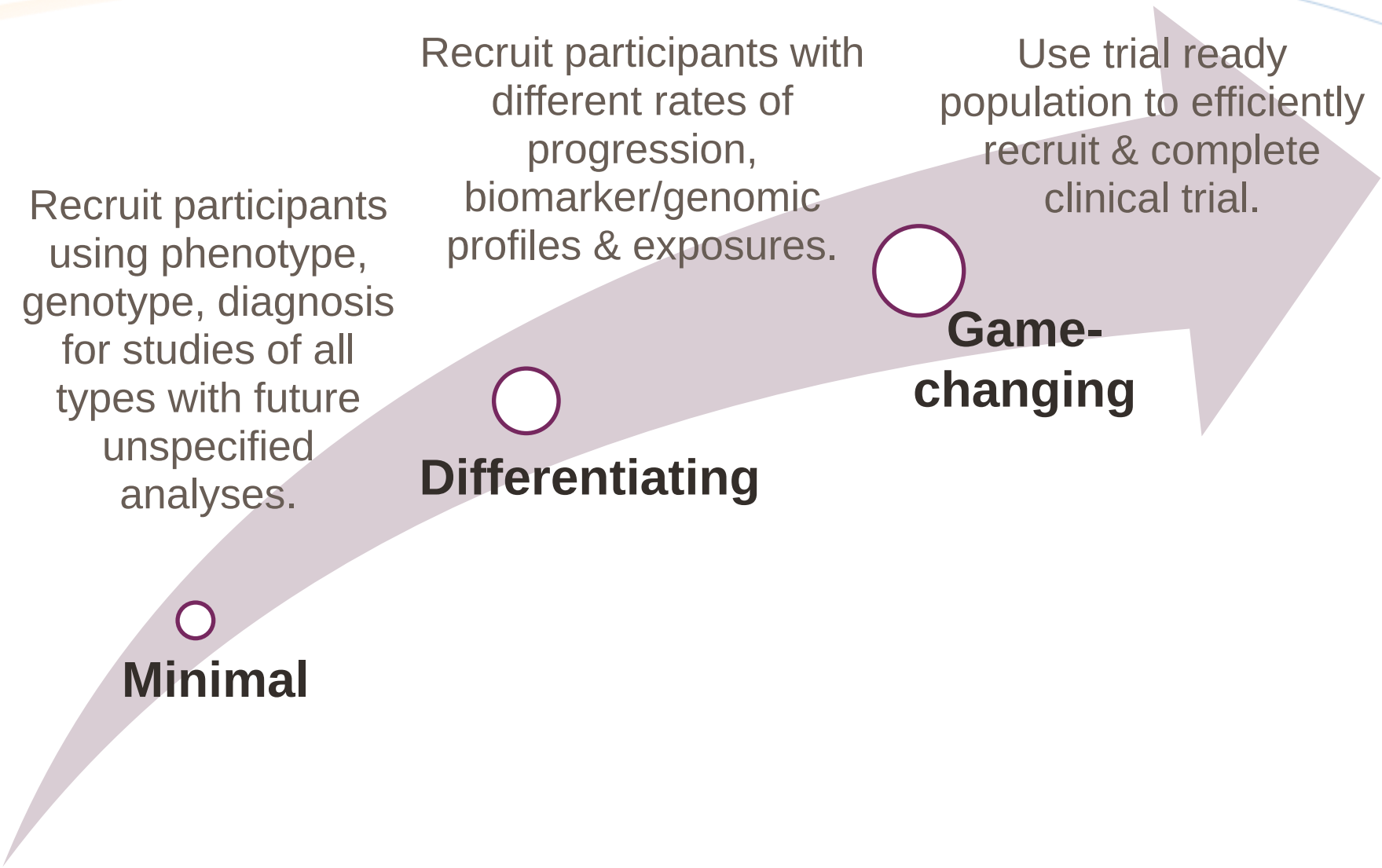
Simulate/predict outcomes/progression when modulating drug target.

Game-changing

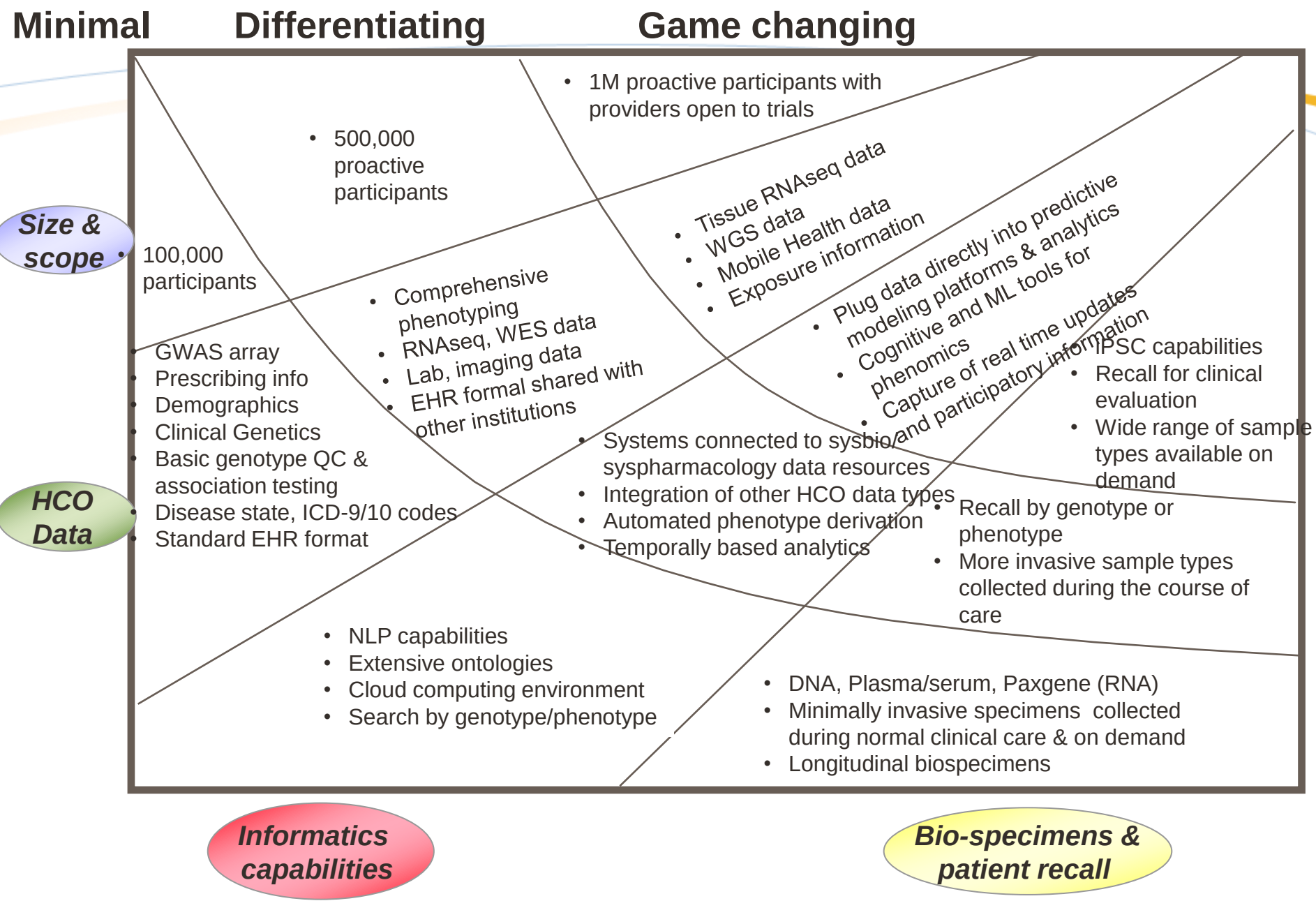
Use of systems biology/systems pharmacology with genetic, frequently sampled clinical, biomarker data.

EMR-Linked Biobanks for Drug Discovery & Development

Human Clinical Trials – Pragmatic Trials



Emerging Requirements for Genomic Resources



Consortium Deliverables: Research-Enabled Environment

- Capability to assess if target is associated with clinical conditions & drug response enabling prediction of possible outcomes.
- Consent and infrastructure to identify and recontact patients for clinical trials of all types using genetic and clinical information
- Access model that enables member companies to easily perform scoping and analysis
- Informatics capabilities that enable harmonization of phenotypes and meta-analysis of results across studies.
- Option to leverage existing or generate additional data for all or sub-sets of the resource (e.g. biomarkers, metabolomics)

Next Steps

- Assemble parties that are interested in participating in the consortium organization/planning phase.

- Work together to answer the question:
  - What are the models that would bring together EMR-linked biobank resources to enable us to achieve our goals of a research enabled environment?

- We intend to develop a business plan and funding model which will realize our goals by the end of 2016.

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- Rebecca Blanchard
- Caroline Fox
- Robert Plenge
- Heiko Runz

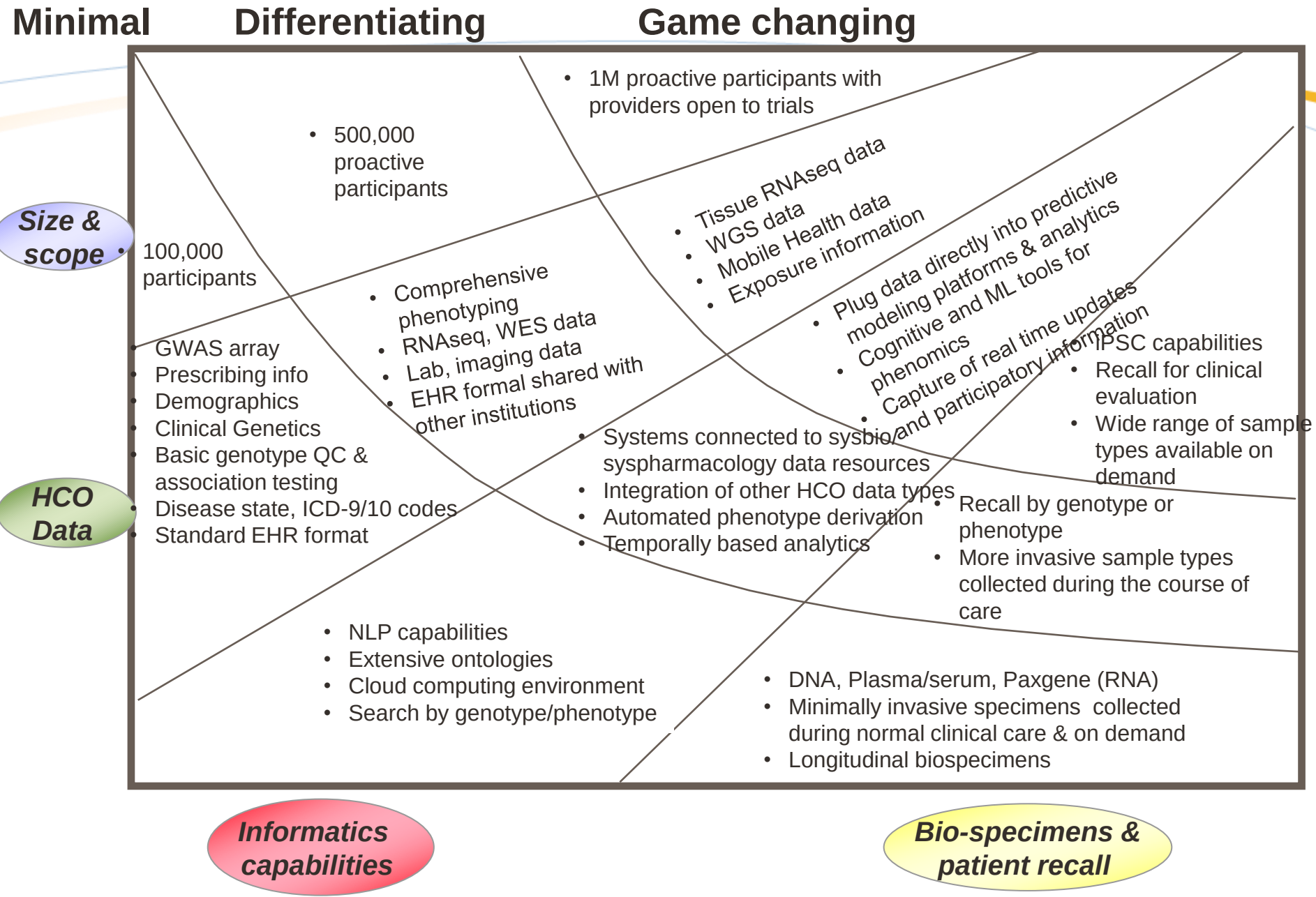
- Nan Bing
- Craig Hyde
- Katrina Loomis
- Cliona Molony
- Serena Scollen
- Jemma Wilk

- Arthur Holden – Co-Chairman of Genomic Resources for Drug Discovery Consortium Organizing Committee

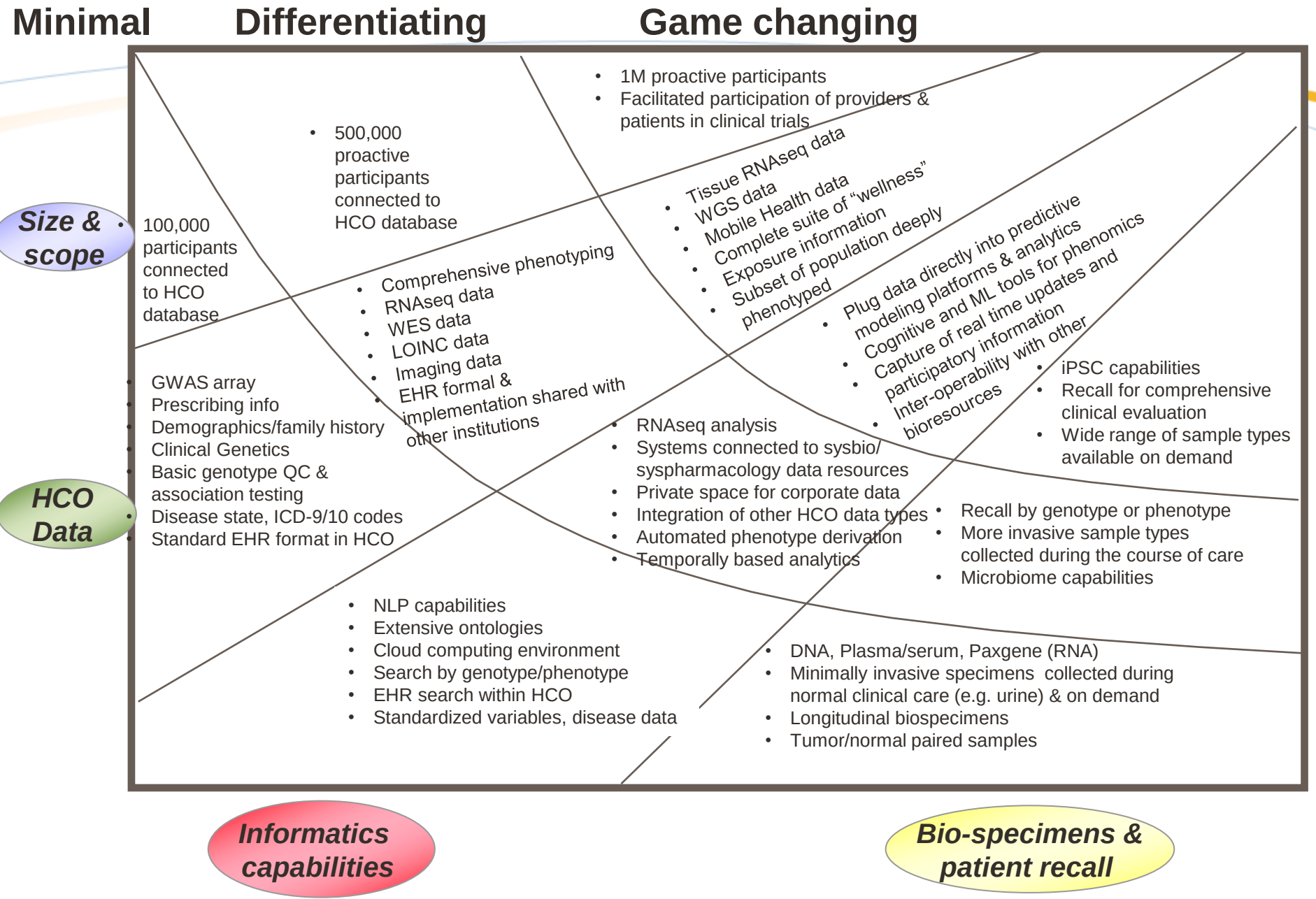
- ***GLP1R* Example**
- Daniel Frietag
- Robert Scott
- Nick Wareham

Back-up Slides

Genomics Resources



Genomics Resources



Questions RWD and Genetics can address

	Discovery – Basic Research / Pre-Clinical Studies	Development – Human Clinical Trials / Pragmatic Trials
Game-changing	– Can we simulate/predict possible outcomes (efficacy and safety) when we modulate a drug target? – Use of systems network biology /systems pharmacology using genetic data, frequently sampled biomarkers and simulated medicine use.	– Use trial ready population to efficiently recruit and complete clinical trial – Detailed natural history data – Imaging data – Cognitive tests on regular basis
Differentiates	– What targets or pathways contribute to disease pathogenesis, progression, complications and recurrence? – What is the evidence that modulating a specific drug target will prevent disease, slow progression or prevent complications? – What is the evidence that diseases (i.e. Cancers) could benefit from alternative or combination treatments?	– Use resource to identify participants with different rates of progression, biomarker profiles, clinical genetic diagnoses, genetic/genomic (germline & somatic) profiles and exposures (family history, taking specific medications, ...) which contribute to an efficient clinical trial. – What are the biomarkers that can track early signs of efficacy in the clinic? – Which biomarkers, clinical phenotypes will select patients most likely to develop severe conditions? – Which biomarkers are prognostic?
Minimal	What is the evidence that a given target /pathway/molecule is associated with clinical conditions using cross sectional data.	– Need to be able to recruit subjects with specific characteristics including phenotype, genotype (germline, somatic), diagnosis for trials/specialized studies with future unspecified analyses.

	Size and Scope	HCO data	Informatics capabilities	Biospecimens and patient recall	Clinical trials
Game changing	• 1M participants • Facilitated participation of health care providers and patients in research and clinical trials	• Tissue RNAseq data • WGS data • Mobile Health data • Complete suite of “wellness” • Exposure information • Subset of population deeply phenotyped	• Plug data directly into predictive modeling platforms and analytics • Cognitive and ML tools for phenomics • Capture of real time updates and participatory information • Inter-operability with other bioresources	• iPSC capabilities • Recall for comprehensive clinical evaluation • Wide range of sample types available on demand	• Disease progression biomarker data • EMRs linked to clinical trial repository with inclusion exclusion criteria information to flag relevant targeted clinical trials
Differentiates	• 500,000 participants • Demographic similarity to target population • Praoctive participants • Ability to contact and recruit subjects into clinical trials	• Comprehensive phenotyping • RNAseq data on some tissues • WES data • LOINC data • Imaging data • EHR formal and implmentation shared with other institutions	• Private space in which to add corporate data • RNAseq analysis • Integration of separately stored HCO data types • Capabilities for temporally based analytics • Systems connected to sysbio/syspharmacology data resources • Automated phenotype derivation for safety and efficacy outcomes	• Recall by genotype or phenotype • More invasive sample types (e.g. CSF, synovial fluid, biopsies) collected during the course of care • Micbrobiome capatillities • Longitudinal biospecimens >15 years	• Rich genomic data collated • Comprehensive clinical , family history and phenotype data • Detailed prescribing information
Minimal	• 100,000 genotyped participants connected to larger HCO database • Consent for specific genotyping & future unspecified research	• Demographics • Genome-wide SNP array • Clinical Genetics if available • Family history where available • Basic genotype QC and association testing • Disease state, ICD-9/10 codes • Detailed prescribing information • Standard EHR format within institution	• Cloud computing environment • Search biorepository by genotype or phenotype • EHR search whether or not genetic data available • Standardized variables, disease definitions • Extensive ontologies • NLP capabilities	• DNA, Plasma/serum, Paxgene (RNA) • Minimally invasive specimens collected during normal clinical care (e.g. urine) and available on demand • Longitudinal biospecimens • Tumor/normal paired samples	• Global network of over 1 Million subjects • Some genotyping and health data • Ability to contact and recruit subjects into clinical trials • Consent for specific genotyping and future unspecified

Name	Objective	Study Design	Deliverables
COPD target validation	Evaluate if variation in respiratory infection/COPD drug targets is associated with susceptibility to bacterial and viral infections.	Develop phenotypes from EMR for exacerbations, streptococcus infection, pneumonia, acute bronchitis and bronchiolitis, bacterial phenumonia, bronchiectasis, influenza, pneumococcal pneumonia, and viral pneumonia as well as other related phenotypes. Perform PheWAS and/or GWAS studies of these phenotypes.	Results would be used to prioritize COPD drug targets that have been identified using phenotypic screens.
GWAS of dermatology conditions	Identify genetic risk factors associated with disease risk or progression for understudied dermatology conditions.	Develop phenotype of interest using EHR data for CD8+ interface dermatitis, neutrophilic dermatoses, hidradenitis suppurativa, rosacea, lichen planus and acne. Perform association analysis of all genetic variants with phenotypes.	Genome wide association results for these diseases will be used to gain insight into disease mechanisms and prioritize drug targets and pathways.
Progression of renal diseases	Identify and study rapid and slow progressors for renal diseases of interest.	Identify and characterize patients who are rapid/slow progressors for diabetic nephropathy, high risk APOL1 CKD and polycystic kidney disease (PKD) using clinical labs (eGFR, albuminuria, albumin/creatinine ratio) and characteristics such ashypertension. Identify if there are genetic differences between the groups.	Results will be used to guide drug discovery efforts for listed diseases.
Study of factors influencing the preservation of muscle mass.	Identify factors influencing muscle mass for patients with COPD	Identify COPD patients that are preserving muscle mass versus those that are failing to preserve muscle mass measured using 6 minute walk test, SPPB, DEXA scan or MRI. Identify factors contributing to preservation of muscle mass.	
Feasibility of PGx study of recently marketed GSK compound	Evaluate the #s of patients taking recently marketed GSK compound that could be enrolled into pharmacogenetic studies.	Develop protocol to assess feasibility of a pharmacogenetic study that would enroll subjects who have taken recently marketed GSK compound and evaluate if genetic variants are associated with drug response.	Study would be focused on replicating results derived from clinical trial study and evaluating if marker could be used to identify responders in a real world setting.
Heart failure (HF) sub-types and disease	Identify and study typical HF patients with reduced ejection fraction (EF)	Identify and characterize HF patients with reduced EF that are progressing most rapidly. Can we identify and characterize patients whose disease is more related to primary cardiac	Results will be used to focus drug discovery and development efforts.